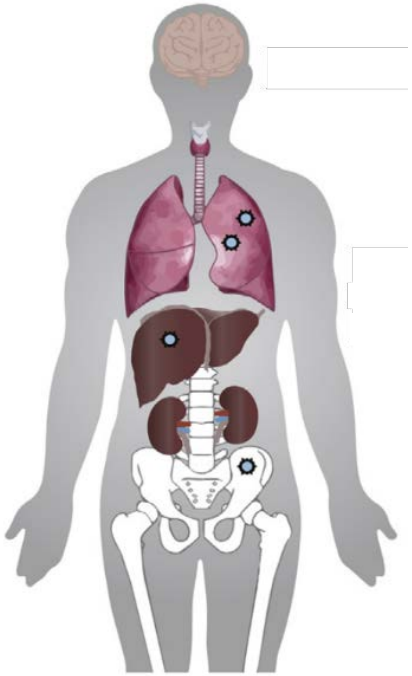
BC CANCER

Provincial Health Services Authority

Stereotactic Ablative Radiotherapy (SABR) for Oligometastatic Disease: Is a New Treatment Paradigm Coming?



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Research Lead, UBC/UNBC Northern Medical Program

MSFHR Health Professional - Investigator

a place of mind UBC

UNBC

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Discover. Connect. Engage.

Disclosures

- I have received funding from Varian Medical Systems (radiation machine manufacturer), which was not related to this research
- I am a skeptic, and was surprised by COMET trial results
  - I was concerned we were overtreating with radiotherapy
- Many of these slides are edited (with permission) from David Palma (London, ON), and Devin Schellenberg (Surrey)

Learning Objectives

- Define the oligometastatic State
- Understand the unique aspects of Stereotactic Ablative Radiotherapy (SABR)
- Review the recent clinical trials of SABR in the oligometastatic state
- Discuss the need for further research for SABR and surgery in the oligometastatic state

Background

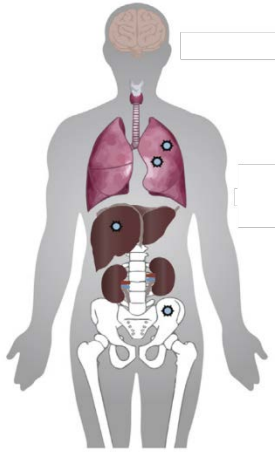
- In BC, we have a unique ability to test radiotherapy techniques, such as SABR, because:
  - We are on salary (no financial incentive)
  - Leaders are constrained by finances (don't have funding for more physicists)
  - We rely on evidence before adopting new techniques
- Other countries are using SABR for oligometastes without these constraints
- Our patients receive these treatments late, in comparison

The Oligometastatic Paradigm

Journal of Clinical Oncology, Vol 13, No 1 (January), 1995: pp 8-10

EDITORIAL

Oligometastases



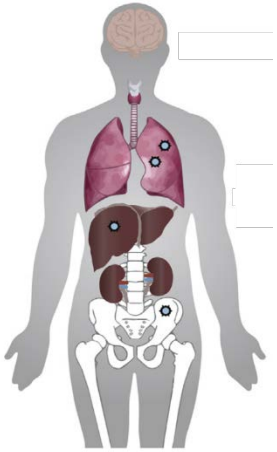
- Term formally named in 1990s[1] but anecdotally reported as early as the 1930s[2]
- Hypothesized some patients could be cured with **surgery & now SABR**

1. Hellman et al, JCO 1995. 2. Barney et al J Urol 1939

The Oligometastatic Paradigm

- Variably defined as patients with
  - A limited (1-3 or 1-5) sites of metastatic disease
  - From primary solid tumours (e.g. breast, colon, prostate, lung)

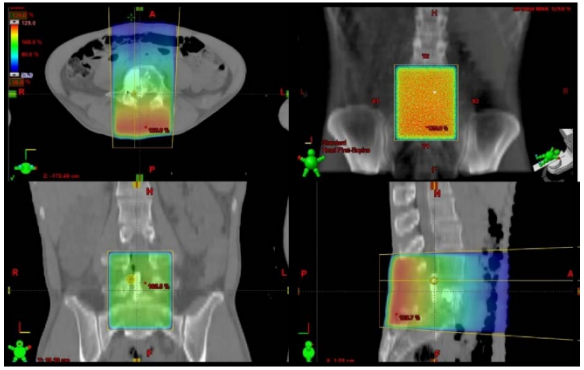
- Historically treated with systemic therapies to delay progression, palliate, and extend life, but not to “cure”
  - Radiotherapy (RT) reserved for palliation at low doses
  - Surgery used in select patients (e.g. colon cancer with liver mets)



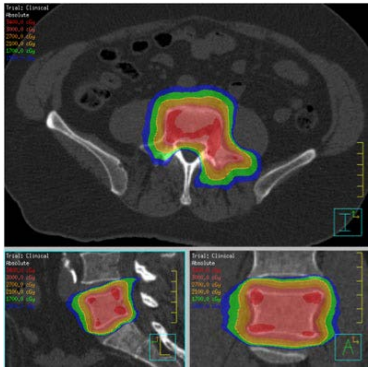
Stereotactic Ablative Radiotherapy (SABR)

- High doses of RT achieved by:
  - Limiting the volumes to highly conformal areas in and around the tumours, while avoiding normal tissues
  - Using imaging devices attached to linear accelerators to position accurately every day

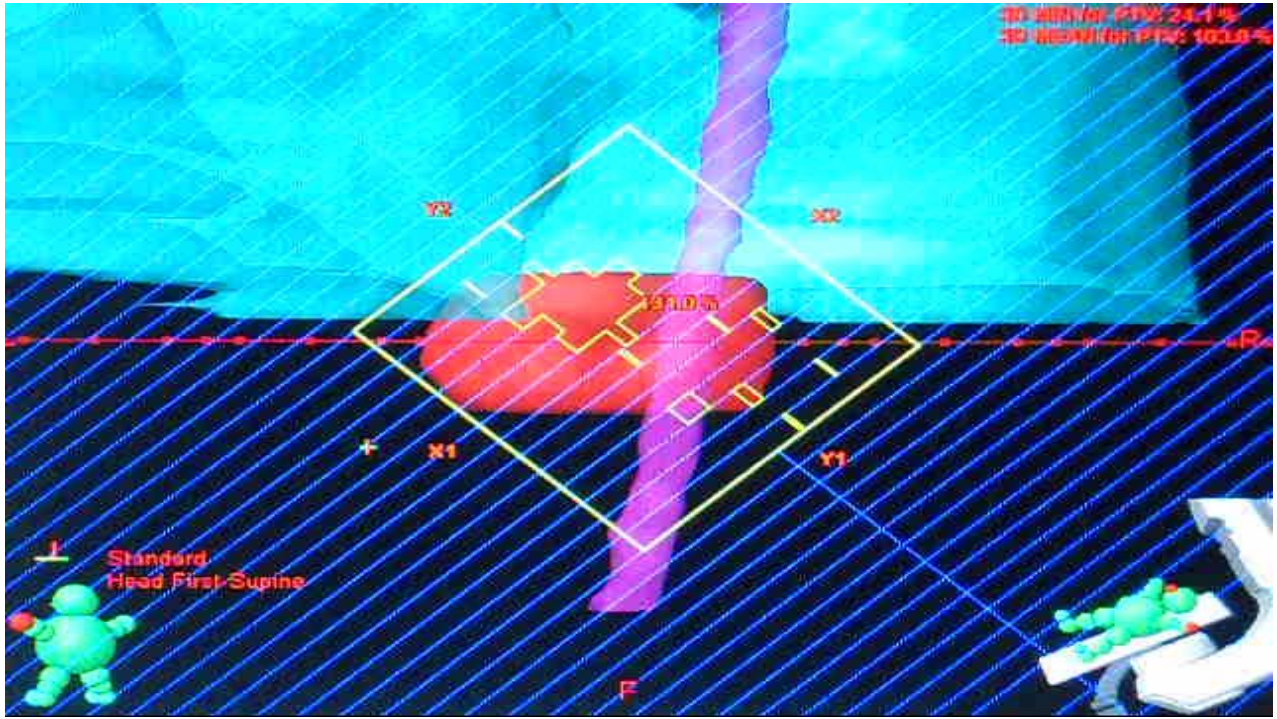
Conventional palliative



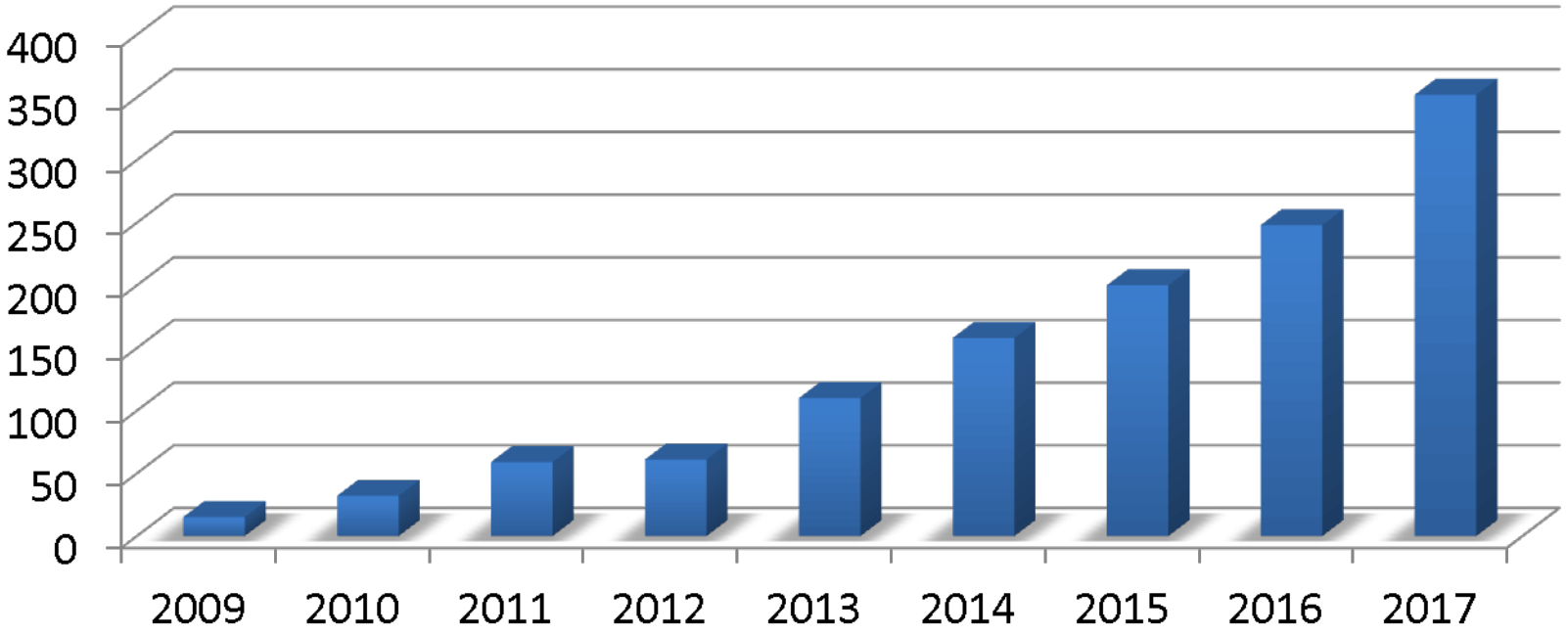
SABR



Volumetric Modulated Arc Therapy



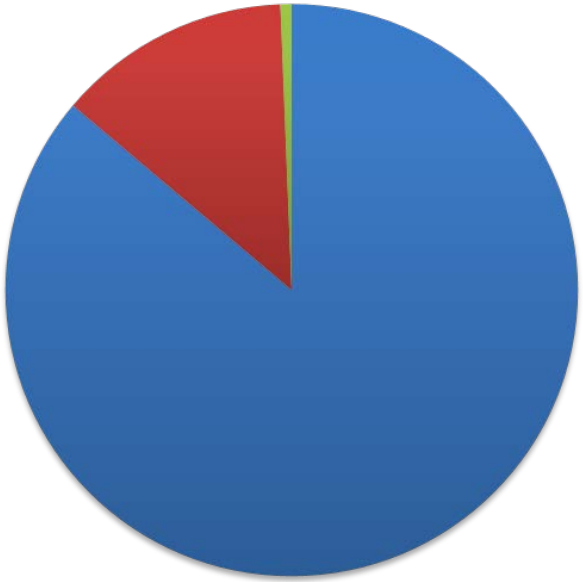
Total Yearly SABR treatments
BC Cancer - Provincially



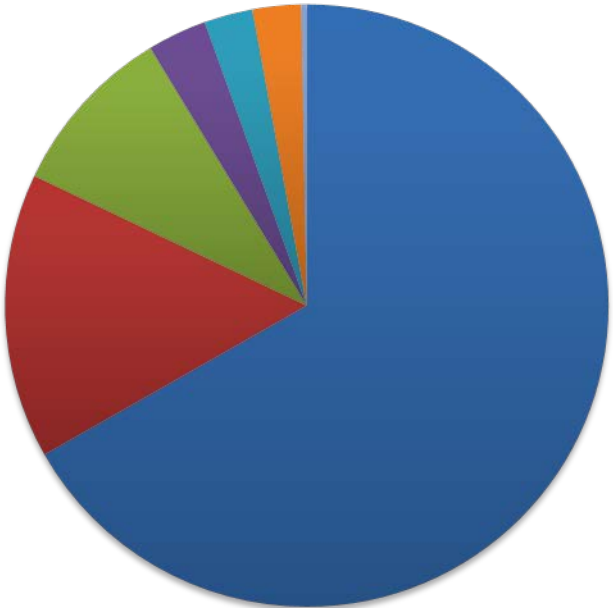
352 in 2017

SABR Distribution (BC wide)

2014



2017



- Lung
- Liver
- Spine
- Bone
- Prostate
- Other
- Adrenal

How is SABR used now in BC?

- Most common indication for SABR is stage I lung cancer
  - Generally confined to patients not fit for surgery
- Also used in primary liver cancer patients who are not surgical candidates
- SABR for body metastases is confined to trials*

SABR-5 phase II trial

- Accruing patients with oligometastases or oligoprogression
- BC only trial, awaiting phase III trials

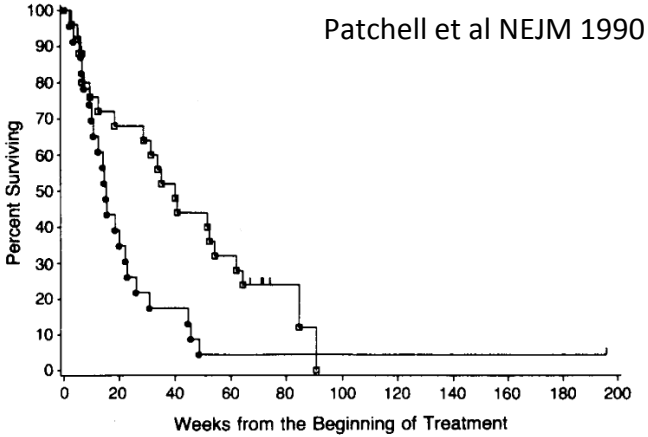
How does SABR compare to surgery?

- The level of evidence does not deserve slides
- In general, both SABR and surgery have great local control
  - Side effect profiles differ; surgery often associated with more morbidity
- We should focus our efforts on when to use our ablative techniques

Level 1 evidence exists for solitary brain mets only

A RANDOMIZED TRIAL OF SURGERY IN THE TREATMENT OF SINGLE METASTASES TO THE BRAIN

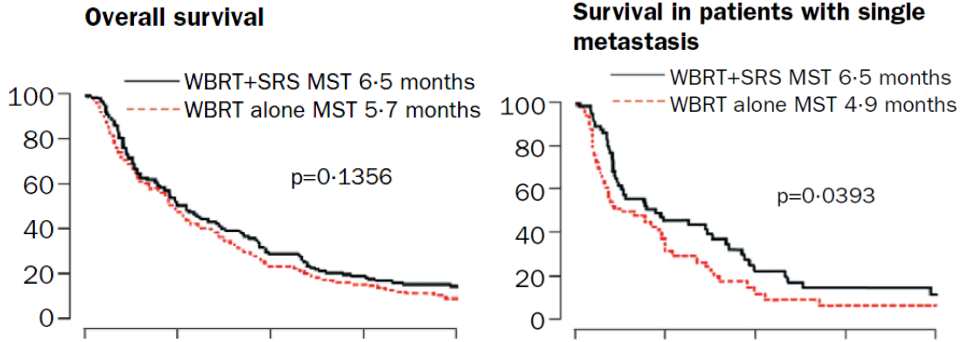
Roy A. Patchell, M.D., Phillip A. Tibbs, M.D., John W. Walsh, M.D., Robert J. Dempsey, M.D., Yosh Maruyama, M.D., Richard J. Kryscio, Ph.D., William R. Markesbery, M.D., John S. Macdonald, M.D., and Byron Young, M.D.



Patchell et al NEJM 1990

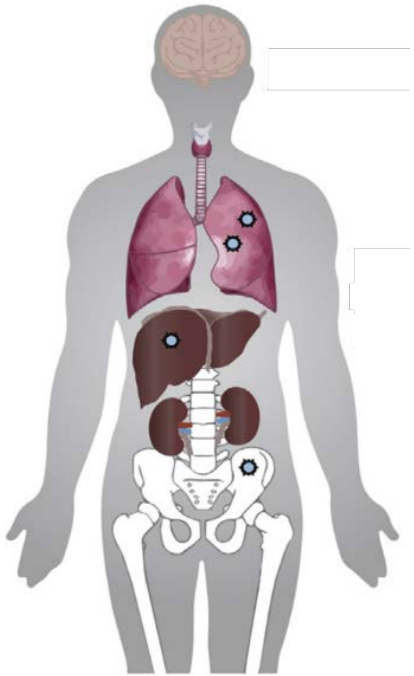
Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

Andrews et al Lancet 2004



Level of evidence for ablation of mets is low

- Outside of the brain
- E.g. there is no level 1 evidence for liver resection



Hepatic Metastectomy

Results of hepatic resection for metastatic colorectal cancer

Author and year	Number of patients	5 yr OS, percent	Median survival, months
Hughes, KS; 1986	607	33	NR
Scheele, J; 1995	434	33	40
Nordlinger, B; 1996	1568	28	NR
Jamison, RL; 1997	280	27	33
Fong, Y; 1999	1001	37	42
Iwatsuki, S; 1999	305	32	NR
Choti, M; 2002	133	58	NR
Abdalla, E; 2004	190	58	NR
Fernandez, FG; 2004	100	58	NR
Wei, AC; 2006	423	47	NR
Rees, M; 2008	929	36	42.5
de Jong, M; 2009	1669	47	36
Morris, EJ; 2010	3116	44	NR

NR: not reported; OS: overall survival.

Morris et al, Brit J Surg, 2010

Lung Metastectomy

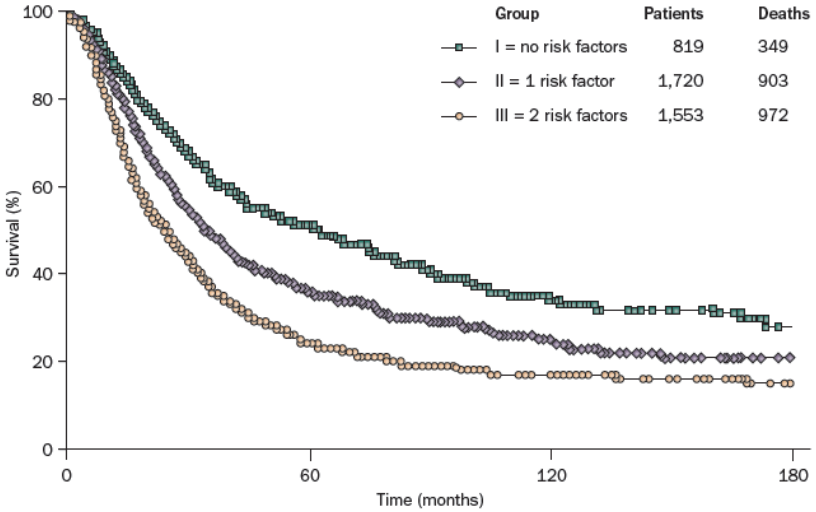


Figure 1 | Survival of patients undergoing pulmonary resection of metastatic tumors. Each curve represents the survival of patients with an increasing number of risk factors for recurrence as determined by a retrospective review of the data.[7] These categories are: group I, a single resectable metastasis with a disease-free interval from primary tumor to metastasis of ≥36 months; group II, multiple metastases or a disease-free interval <36 months; group III, multiple metastases and a disease-free interval <36 months. The size, number and tumor type are risk factors for recurrence. Permission obtained from Elsevier © Pastorino, U. *et al. J. Thorac. Cardiovasc. Surg.* **113**, 37–49 (1997).

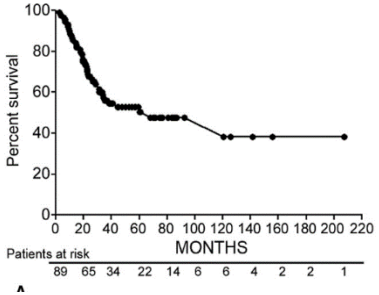
Weichselbaum and Hellman, Nat Rev Clin Onc 2011

Other Histologies

Pulmonary Resection of Metastatic Sarcoma: Prognostic Factors Associated With Improved Outcomes

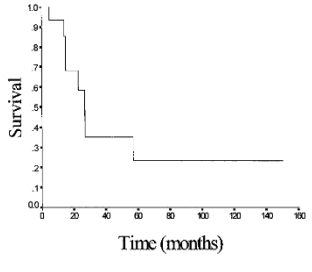
Samuel Kim, MD, Harald C. Ott, MD, Cameron D. Wright, MD, John C. Wain, MD, Christopher Morse, MD, Henning A. Gaissert, MD, Dean M. Donahue, MD, Douglas J. Mathisen, MD, and Michael Lanuti, MD

Division of Thoracic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts



Liver metastases from breast cancer: Long-term survival after curative resection

Markus Selzner, MD, Michael A. Morse, MD, James J. Vredenburgh, MD, William C. Meyers, MD, *and* Pierre-Alain Clavien, MD, PhD, *Durham, NC*

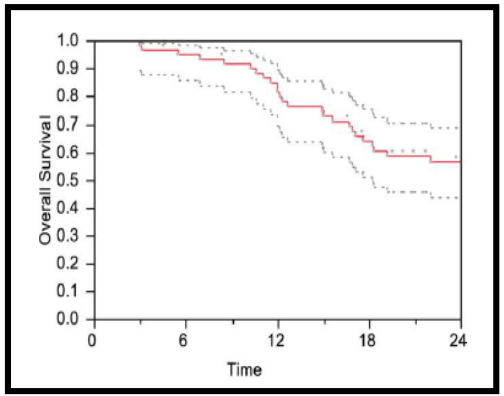


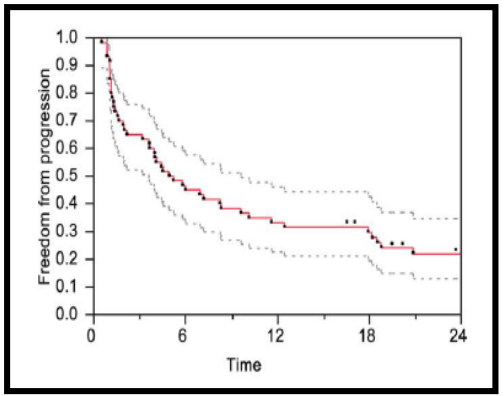
SABR for Oligometastatic Disease

Stereotactic Body Radiotherapy for Multisite Extracranial Oligometastases

Final Report of a Dose Escalation Trial in Patients With 1 to 5 Sites of Metastatic Disease

Joseph K. Salama, MD[1]; Michael D. Hasselle, MD[2]; Steven J. Chmura, MD, PhD[2,3]; Renuka Malik, MD[2]; Neil Mehta, MD[2]; Kamil M. Yenice, MD[2]; Victoria M. Villaflor, MD[3,4]; Walter M. Stadler, MD[3,4]; Philip C. Hoffman, MD[3,4]; Ezra E. W. Cohen, MD[3,4]; Philip P. Connell, MD[2,3]; Daniel J. Haraf, MD[2,3]; Everett E. Vokes, MD[2,3,4]; Samuel Hellman, MD[2]; and Ralph R. Weichselbaum, MD[2,3,5]





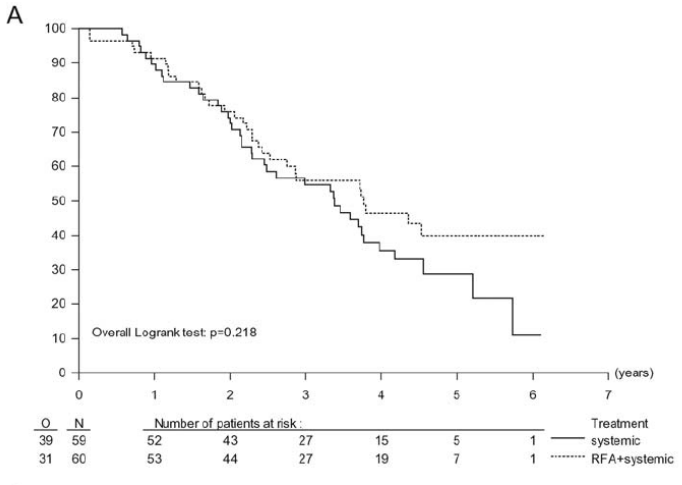
The Evidence Looks Good,

…But:

- Nearly all studies are single-arm studies
- Appropriate controls lacking
- Selection of very fit patients
- Slow tumor doubling times
- Immortal Time Bias

Radiofrequency Ablation

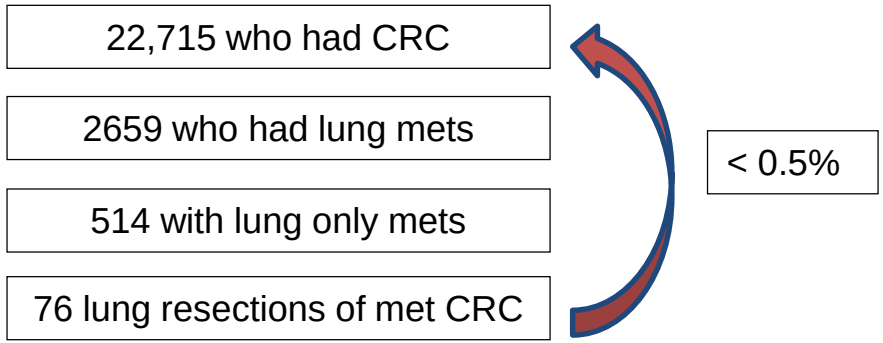
Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004)



Ruers et al, Ann Oncol 2012

Is it all selection bias and slow doubling time?

- Most ablative series (surgery, RFA, SABR) report on a small subset of patients, and rarely report on the size of the POPULATION from which they are drawn
- EXCEPTION: Wade *et al* (1996): 36% 5 yr survival after lung met resection from CRC



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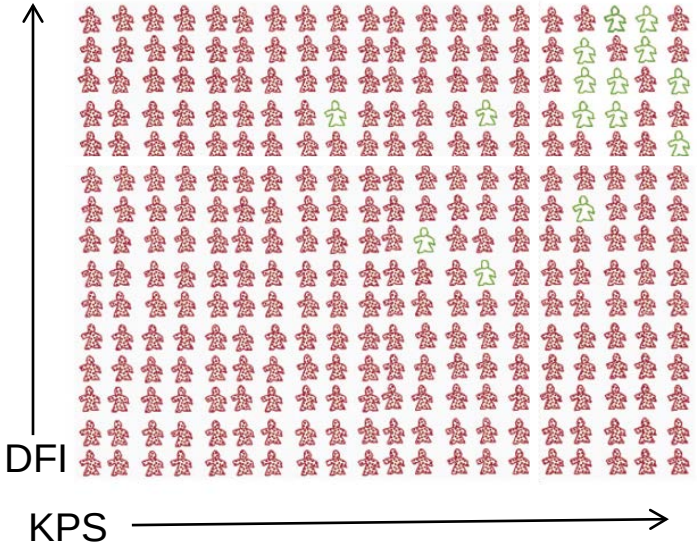
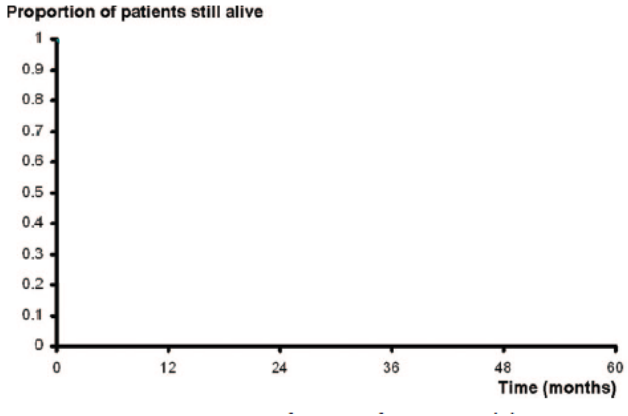
Is it all selection bias and slow doubling time?





Population: 5% alive

Among long DFI and good KPS: 40% alive

Utley and Treasure, JTO 2010

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What's the harm?

Surgical Resection of Pulmonary Metastases From Colorectal Cancer: A Systematic Review of Published Series

Joachim Pfannschmidt, MD, PhD, Hendrik Dienemann, MD, PhD, and Hans Hoffmann, MD, PhD

Department of Thoracic Surgery, University of Heidelberg, Heidelberg, Germany

Table 1. Studies Reporting on Patients With R0 Resections

Author Institution	Recruitment Period	Selection of Patients	Characteristics of Patients	Median Follow-up (mos)	Postoperative Mortality	5-Year Survival, R0 (%)	Median Survival (mo)
Higashiyama Osaka, 2003 [13]	1981–2001	R0:94 patients, R1/:6 patients	n = 100; age range, 39–79 yrs Mean, 60.3 yrs Men, 61; women, 39	30.3	NR	52.3	
Lee Seoul 2006 [18]	1994–2004	R0 only	n = 59; age range, 33–76 yrs Mean age, 55 yrs Men, 39; women, 20	34.7	0%	50.3	NR
Melloni Milan, 2006 [19]	1991–2004	R0:74 patients, R1:7 patients	n = 31; age range, 38–83 yrs Median, 61 yrs Men, 49; women, 32	20	30 days: 0%	44	37
Moore Sydney, 2001 [20]	1984–1997	R0:41 patients, R1/:6 patients	n = 47; age mean, 65 yrs Men, 24; women, 23	21	1/47, 1.7%	24	R0: 28
Pfannschmidt Heidelberg, 2003 [21]	1985–2000	R0 only	n = 167; age range, 25–81 yrs Median, 60.2 yrs Men, 103; women, 64	58.6	30 days: 3/167, 1.8%	32.4	40.2
Rena Torino, Novara, 2002 [22]	1980–2000	R0:71 patient, R1:9 patients	n = 80; age range, 38–79 yrs Median, 63 yrs Men, 37; women, 43	26.8 mean	2/80, 2.02%	41	26.8 mean
Saito Osaka, 2002 [23]	1990–2000	R0 only	n = 165; age range, 33–84 yrs Median, 61.6 yrs Men, 97; women, 68	56.5	0%	39.6	
Sakamoto Akashi, 2001 [24]	1986–2000	R0 only	n = 47; age range, 40–80 years Median, 61 yrs	NR	1/47, 1.7%	48	

ATS 2007

Stereotactic Body Radiation Therapy for Extracranial Oligometastases: Does the Sword Have a Double Edge?

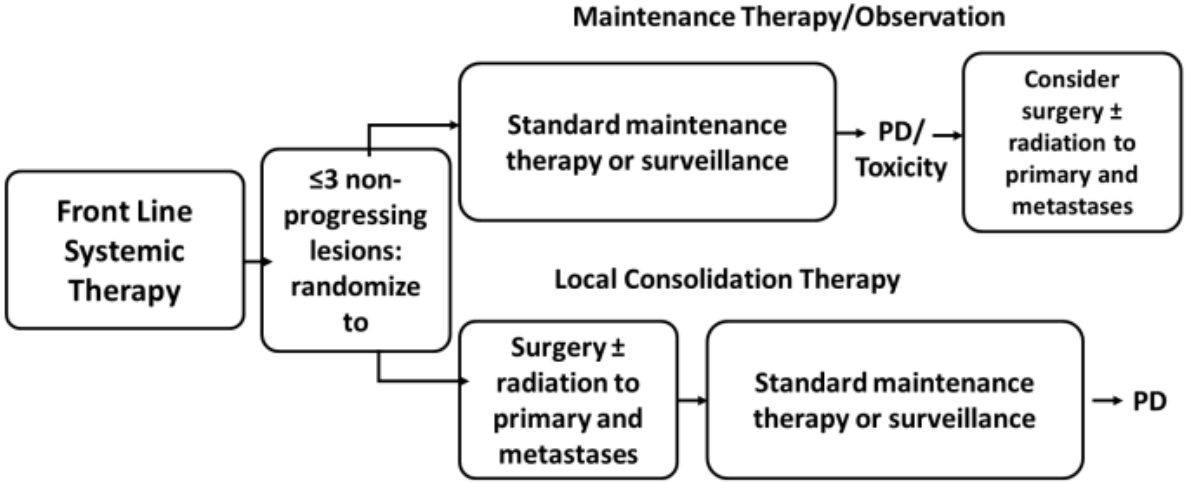
Madeleine Carey Sampson, MD, Alan Katz, MD, MPH, and Louis S. Constine, MD

Table 3 Lung SBRT Literature Results[21–36]

Author	No. of Patients	% NSCLC (v mets) (%)	Median Lesion Size (mL)	Total dose (Gy)	Crude Local Control (LC) (%)	Median Follow-up Time in months (range)	Acute Toxicity (Grade 1–2) (%)	Acute Toxicity (Grade 3–5) (%)	Chronic Toxicity (Grade 3–5) (%)
Blomgren et al[21]	13	18	48 mL	15–45	94	8.2	NR	NR	6
Uemetsu et al[22]	45	35	7.2 mL* (mean)	30–75	97	11	11	0	0
Wulf et al[23]	26	44	57 mL	30	85	8	22	0	7 1 death
Nakagawa et al[24]	15	5	Lung 4.5 mL (CW 40 mL)	15–25	95	10	0	0	0
Fukumoto et al[25]	22	100	10 mL*	48–60	94	24 (2–44)	27	0	0
Nagata et al[26]	40	78	12.6 mL	40–48	94 lung ca) 67 (mets)	18–19	NR	0	0
Hof et al[27]	10	100	12 mL	19–26	80	14.9	0	0	0
Timmerman et al[28]	37	100	22.5 mL	24–60	84 (resp 87)	15.2	49	8	0
Hara et al[29]	23	22	5.8 mL (mean)	20–30	83	13	13	4	0
Lee et al[30]	28	32	41.4 mL (PTV)	30–40	89	18	0	0	0
Onimaru et al[31]	45	57	9.2 mL*	48–60	88	17	4	2 1 death	0
Uematsu et al[32,33]	50	100	17 mL*	50–60	94	60	16	0	0
Whyte et al[34]	23	65	NR (range 0.5–65 mL*)	15	~91 (2/23 PD, NR)	7	0	0	0
Onishi et al[35]	245	100	11.5 mL*	18–75	85.5	24	11	4	1.2
Wulf et al[36]	61	33	22 mL	10–26	95 (lung ca) 90 (mets)	9–11	16	0	0

Randomized Data is emerging for lung cancer

- Gomez (MD Anderson); phase II; closed early (n=49)
- Stage IV; synchronous oligometastases (</= 3)
- After systemic therapy



Crossover allowed at the time of progression

Randomized Data is emerging for lung cancer

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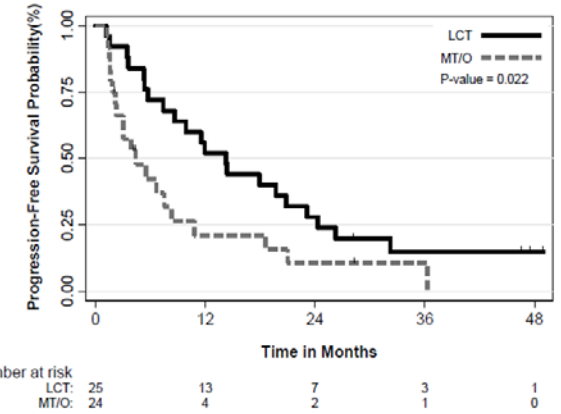
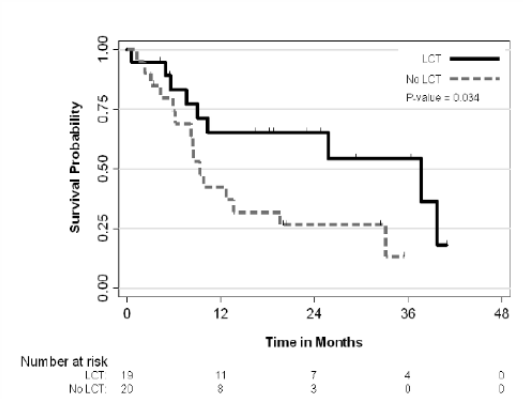
Progression Free Survival



Median PFS
LCT = 14.2 months
MT/O = 4.4 months

Statistically significant
P = 0.022

Survival After Progression



Median 37.6 months LCT [95% CI 9.0-not reached] vs. 9.4 months MT/O [95% CI 5.9–19.6, *P*=0.034]

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COMET trial results, which BC participated in..

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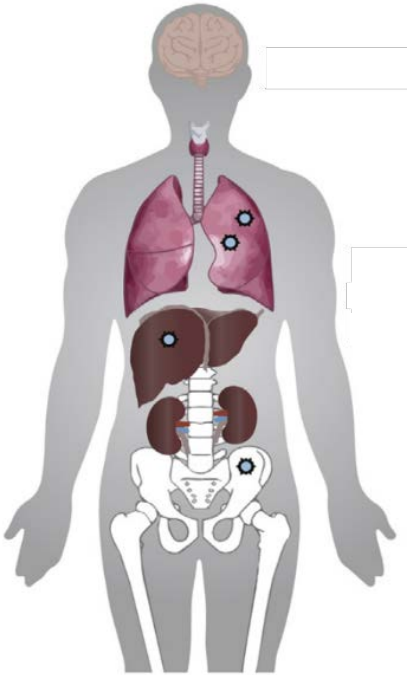
OICR
Ontario Institute for Cancer Research

SABR-COMET: Stereotactic Ablative Radiation (SABR) for the Comprehensive Treatment of Oligo-metastatic Cancers – Results of a Randomized Study

D. Palma, R. Olson, S. Harrow, S. Gaede, A. Louie, C. Haasbeek, L. Mulroy, M. Lock, G. Rodrigues, B. Yaremko, D. Schellenberg, B. Ahmad, G. Griffioen, S. Senthi, A. Swaminath, N. Kopek, M. Liu, K. Moore, S. Currie, G. Bauman, A. Warner, S. Senan



Endpoints

Primary Endpoint

- Overall Survival

Secondary endpoints:

- Progression-free survival
- Toxicity (CTC-AE 4.0)
- Quality of life (FACT-G)
- Lesional control rate
- Number of cycles of further systemic therapy

Main Inclusion Criteria

- Controlled primary tumor
  - defined as: at least 3 months since original tumor treated definitively, with no progression at primary site
- Up to to 5 metastases Most were 1-2
- Maximum 3 metastases in any single organ system
- All sites of disease safely treatable

Phase II Randomized Screening Design

VOLUME 23 · NUMBER 28 · OCTOBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

Design Issues of Randomized Phase II Trials and a Proposal for Phase II Screening Trials

Lawrence V. Rubinstein, Edward L. Korn, Boris Freidlin, Sally Hunsberger, S. Percy Ivy, and Malcolm A. Smith

- Moderate sample size to provide an initial, non-definitive comparison between two arms
- Once trial is complete, a finding can be considered definitive if $p<0.005$

Phase III RCT alpha = 0.05

Phase II Screening RCT alpha = 0.20

SABR Details

- Number of fractions dependent on tumor size and location
  - Lung: 54/3, 55/5, 60/8
  - Bone: 35/5, 30/3, 16-20/1
  - Brain: SRS (18-24/1) or SABR (40/5), WBRT optional
  - Liver: 45-60 Gy in 3-8
  - Adrenal: 60/8

Big doses in comparison to adjuvant/curative

- Normal tissue tolerances <u>not to be exceeded</u>
  - PTV coverage compromised wherever needed

Unique
Not possible in surgical trials

Sample Size and Analyses

- Estimated median survival of 9 months in control arm. To detect a 6-month improvement in OS, with 80% power, a two-sided alpha of 0.2, and 5% rate of dropout, 99 patients needed.
- All analyses **intention-to-treat** and **pre-specified**
- Protocol assumed 4 years of accrual and 1 year of additional follow-up. Data locked as of Jan 2018 for this analysis.

Results

Baseline Characteristics

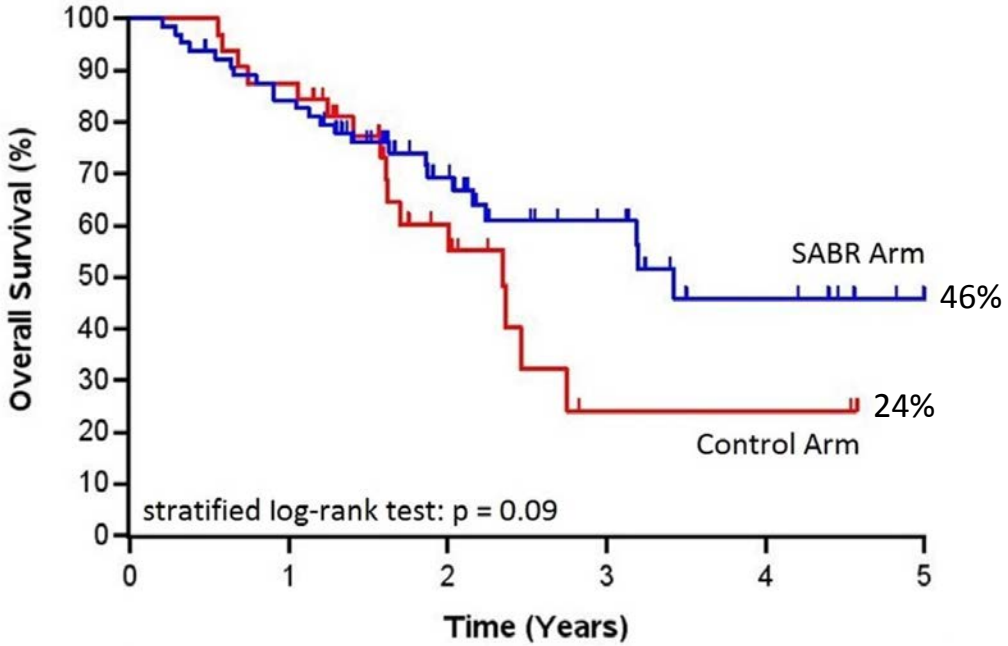
Between February 2012 and August 2016, 99 patients were randomized at centres in Canada, Scotland, Netherlands and Australia

Characteristic	All Patients (n=99)	Control Arm (n=33)	SABR Arm (n=66)	p-value
Age – median, (min, max)	68 (43, 89)	69 (44, 87)	67 (43, 89)	0.494
Sex – n(%)				0.772
Male	59 (59.6)	19 (57.6)	40 (60.6)	
Female	40 (40.4)	14 (42.4)	26 (39.4)	
Site of Original Primary Tumor – n(%)				0.204
Breast	18 (18.2)	5 (15.2)	13 (19.7)	
Colorectal	18 (18.2)	9 (27.3)	9 (13.6)	
Lung	18 (18.2)	6 (18.2)	12 (18.2)	
Prostate	16 (16.2)	2 (6.1)	14 (21.2)	
Other	29 (29.3)	11 (33.3)	18 (27.3)	

Baseline Characteristics

Characteristic	All Patients (n=99)	Control Arm (n=33)	SABR Arm (n=66)	p-value
Number of Metastases – n(%)				0.591
1	42 (42.4)	12 (36.4)	30 (45.5)	
2	32 (32.3)	13 (39.4)	19 (28.8)	
3	18 (18.2)	6 (18.2)	12 (18.2)	
4	4 (4.0)	2 (6.1)	2 (3.0)	
5	3 (3.0)	0 (0.0)	3 (4.6)	
Location of Metastases – n(%)				0.181
Adrenal	9 (4.7)	2 (3.1)	7 (5.5)	
Bone	65 (34.0)	20 (31.3)	45 (35.4)	
Liver	19 (10.0)	3 (4.7)	16 (12.6)	
Lung	89 (46.6)	34 (53.1)	55 (43.3)	
Other	9 (4.7)	5 (7.8)	4 (3.2)	

Overall Survival



Number at risk:

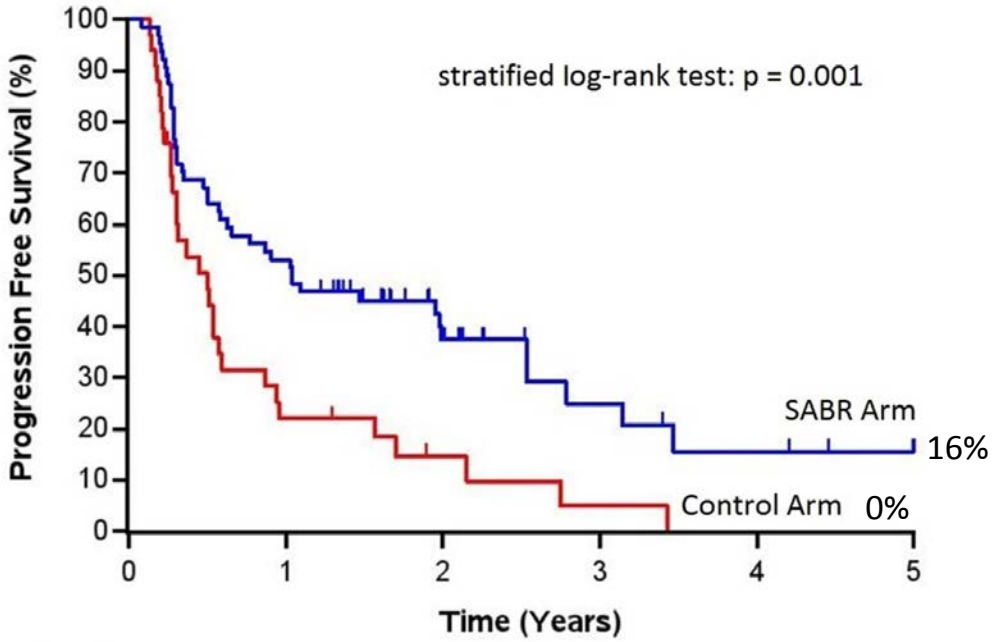
Control	33	28	12	2	2	
SABR	66	53	29	15	7	1

Median OS

Control Arm: 28 months
(95% CI: 19-33 months)

SABR Arm: 41 months
(95% CI: 26 months to 'not reached')

Progression-Free Survival



Number at risk:

Control	33	7	3	1		
SABR	66	34	15	6	3	1

Median PFS

Control Arm: 6 months
(95% CI: 3.4-7.1 months)

SABR Arm: 12 months
(95% CI: 6.9-30 months)

Adverse Events

Characteristic	All Patients (n=99)	Control Arm (n=33)	SABR Arm (n=66)	p-value
Related AE Grade ≥ 2 – n(%)	22 (22.2)	3 (9.1)	19 (28.8)	0.03
AE Associated with Death (Grade 5) – n(%)	3 (3.0)	0 (0.0)	3 (4.5)	0.55
Fatigue – n(%)				
Grade 2	6 (6.1)	2 (6.1)	4 (6.1)	0.45
Grade 3	1 (1.0)	1 (3.0)	0 (0.0)	
Dyspnea – n(%)				
Grade 2	1 (1.0)	0 (0.0)	1 (1.5)	1.00
Grade 3	1 (1.0)	0 (0.0)	1 (1.5)	
Pain (any type) – n(%)				
Grade 2	5 (5.1)	0 (0.0)	5 (7.6)	0.14
Grade 3	3 (3.0)	0 (0.0)	3 (4.6)	

Related Events as determined by the treating investigator (Possibly, Probably, or Definitely Related)

Additional Secondary Endpoints

	Control	SABR	P-value
QOL - FACT-G @ 6 months (mean ± SD)	82.5 ± 16.4	82.6 ± 16.6	0.99

Sensitivity Analyses (not pre-specified)

1) Excluded all prostate patients to see if HR for OS and PFS remain <1
   - OS HR = 0.83
   - PFS HR = 0.61

2) Multivariable analyses for OS and PFS (to control for histology):

OS		
Factor	HR	P-value
Lung Primary (vs. other)	4.05	<0.001
SABR Arm (vs control)	0.60	0.12

PFS		
Factor	HR	P-value
Prostate Primary (vs. other)	0.14	<0.001
SABR Arm (vs control)	0.58	0.02

Discussion

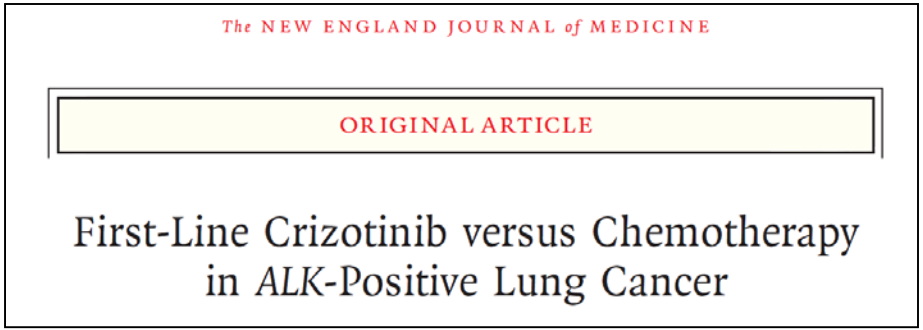
Limitations

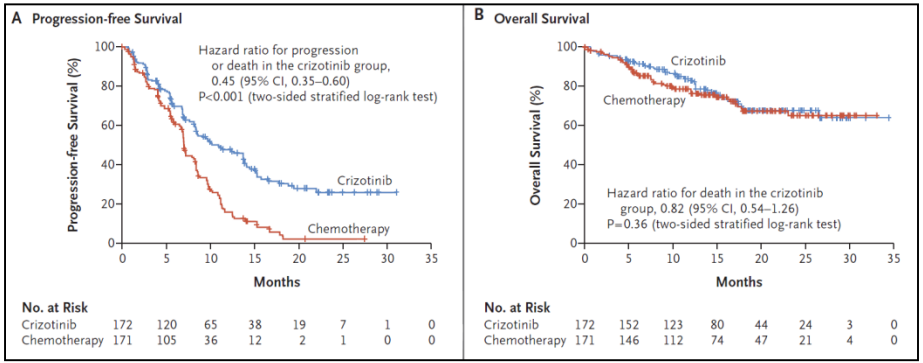
- **Not Histology Specific**
  - Most SRS/SABR trials for metastases are not (brain, spine)
  - Histology specific trials have not accrued well, as numbers are lower
- **Pragmatic Selection of Systemic Agents**
  - It was impossible to mandate specific systemic therapy, given the multiple disease sites and expected changes in SOC over time
- **Phase II Design**
  - OS results not definitive

Is a Clear PFS Benefit Enough to Treat?

- There is ample precedent in oncology
  - Aromatase Inhibitors for Breast Cancer
  - Crizotinib in ALK-rearranged NSCLC

- Majority of FDA approvals for cancer drugs are not based on OS.[1,2]





1. Brooks et al, Drugs Context, 2017
2. Kim et Prasad, JAMA Internal Medicine 2015

Next Steps

SABR-COMET 3

Phase III RCT for patients with a controlled primary tumor and 1-3 metastatic lesions

PI: Robert Olson

SABR-COMET 10

Phase III RCT for patients with a controlled primary tumor and 4-10 metastatic lesions

PI: David Palma

COMET-3 Funding

- Varian granted $500K last week
- BC Cancer Foundation has committed to helping with staff support

COMET-3: BCCF support

- I was prepared to give a short 2 minute blurb on why the Precision Radiotherapy fundraising goal was a priority
- I did not know what was being unveiled

COMET-3 Funding

Provincial Health Services Authority

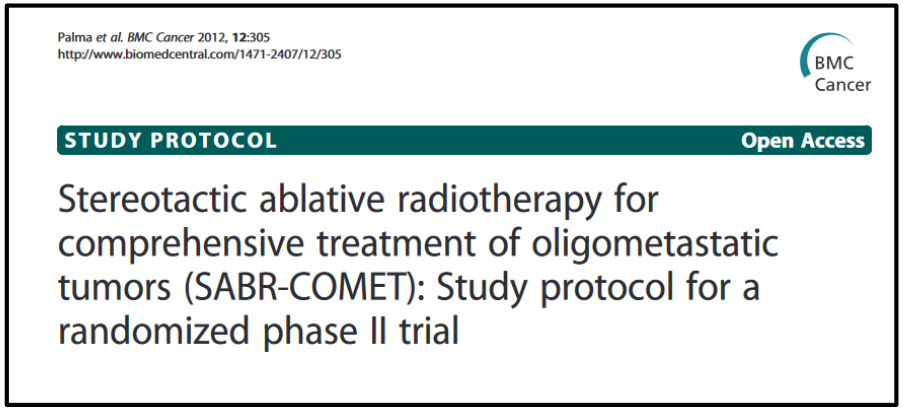
Tue, Nov 27, 6:13 PM

Ha ha . We are on the wall!

Oh dear, that is terrible! I wish someone would have asked me if I wanted my love handles enlarged and hung on the wall at the place of my employment. 😂

Further Information

Protocol



BMC Cancer 2012, 12:305

(open access)

Manuscript

In Press

Conclusions

- Evidence for the use of SABR in the setting of oligometastatic disease is emerging
  - Could be Paradigm changing
  - But there is a real risk of side effects; even mortality
  - I believe we should continue to treat these patients on trial and in a well coordinated provincial program, with robust peer-review and QA
- But, patients (and medical oncologists) might start asking for this treatment off-trial
  - Should we?
  - Do we have the resources in BC to treat?